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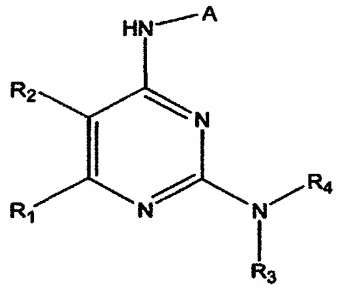
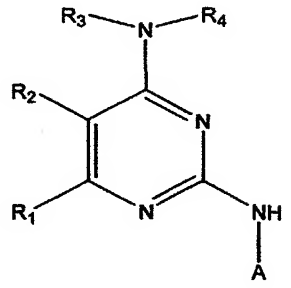
(54) Title: 2,4-DIAMINO-PYRIMIDINE DERIVATIVE COMPOUNDS AS INHIBITORS OF PROLYLPEPTIDASE, INDUCERS OF APOPTOSIS AND CANCER TREATMENT AGENTS



(I)



(II)

(57) Abstract: Compounds which are 2,4-diamino-pyrimidine derivatives of formula (I) or (II), wherein A, R1, R2, R3, and R4 are described in the specification. These compounds are useful for the inhibiting prolylpeptidase, inducing apoptosis and treating cancer.

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2,4-Diamino-Pyrimidine Derivative Compounds as Inhibitors of Prolylpeptidase, Inducers of Apoptosis and Cancer Treatment Agents

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DESCRIPTION OF THE INVENTION

The present invention relates to:

(1) 2,4-diamino-pyrimidine derivative compounds or purified stereoisomers or stereoisomer mixtures of said compounds and salts or prodrug forms thereof;

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(2) pharmaceutical compositions comprising one or more of the compounds or purified stereoisomers or stereoisomer mixtures of the invention, or their salts or prodrugs forms thereof, with a pharmaceutically acceptable ingredient;

(3) methods of preparing the 2,4-diamino-pyrimidine derivative compounds of (1); and

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(4) methods for inhibiting prolylpeptidase, inducing apoptosis and treating cancer in mammals by administering an effective amount of (1) or (2) to a patient in need thereof.

Description of the Compounds

The compounds described as being part of the invention are 2,4-diamino-pyrimidine derivative compounds which have the structural formula (I) or (II) defined below:

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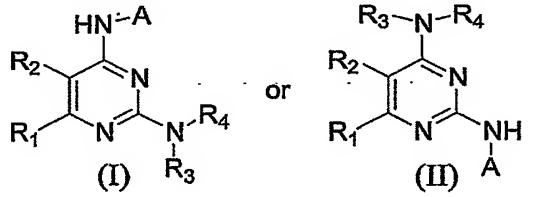

wherein,

R_1 and R_2 are independently selected from the group consisting of hydrogen, halogen, hydroxy, -(C_1-C_3)-alkyl, (C_1-C_5) alkoxy- and -$(CH_2)_nC(=O)OR_7$;

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R_3 is hydrogen;

R_4 is selected from the group consisting of:

(a) -(C_1-C_5) linear or branched alkyl,

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(b) -(C_3-C_{10}) cycloalkyl,

(c) -(C_1-C_5)-alkyl-(C_6-C_{10}) aryl, and

(d) -(C_6-C_{10}) aryl,

wherein (a) - (d) are optionally substituted with one to three substituents selected from the group consisting of:

(1) amino,

(2) cyano,

(3) halogen,

(4) hydroxy,

(5) nitro,

(6) (C_1-C_5) alkoxy-,

(7) -(C_6-C_{10}) aryloxy-,

(8) -(C_1-C_5) alkylamino,

(9) -(C_1-C_5) linear or branched alkyl optionally substituted by halogen,

(10) -$(CH_2)_nC(=O)R_7$,

(11) -$(CH_2)_nC(=O)OR_7$,

(12) -$(CH_2)_nC(=O)NR_8R_9$,

(13) a four to eight membered saturated or fully unsaturated heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, (C_1-C_5) alkoxy-, -(C_1-C_5) alkylamino and (C_1-C_5) linear or branched alkyl optionally substituted by halogen; and

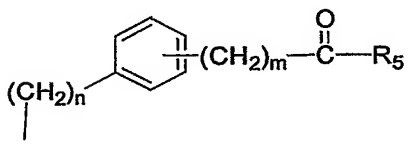
(14) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated four to eight membered heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom, and the other ring is a saturated or fully unsaturated three to eight membered carbocycle,

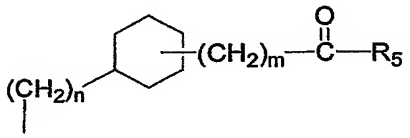
or

R_3 and R_4 form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom and wherein said ring is optionally substituted with up to three substituents selected from the group consisting of:

(1) amino,
(2) cyano,
(3) halogen,
(4) hydroxy,
(5) nitro,
(6) (C_1-C_5) alkoxy-,
(7) -(C_1-C_5) alkylamino,
(8) -(C_1-C_5) linear or branched alkyl optionally substituted by halogen or (C_1-C_5) alkoxy-,
(9) $-(CH_2)_nC(=O)R_7$,
(10) $-(CH_2)_nC(=O)OR_7$, and
(11) $(CH_2)_nC(=O)NR_8R_9$;

A is either:



or


R_5 is -OH, $-OR_6$ or $-NR_8R_9$;

R_6 is:

(a) -(C_1-C_5) linear or branched alkyl optionally substituted by halogen, or
(b) -(C_6-C_{10}) aryl optionally substituted by halogen;

R_7 is:

(e) hydrogen,

(f) -(C_1-C_5) linear or branched alkyl, or

(g) -(C_6-C_{10}) aryl,

wherein (f) and (g) are optionally substituted with halogen;

R_8 and R_9 are independently selected from the group consisting of:

(h) hydrogen,

(i) -(C_1-C_5) linear or branched alkyl, and

(j) -(C_6-C_{10}) aryl;

wherein (i) and (j) are optionally substituted with halogen;

n and m are independently an integer from 0 - 1,

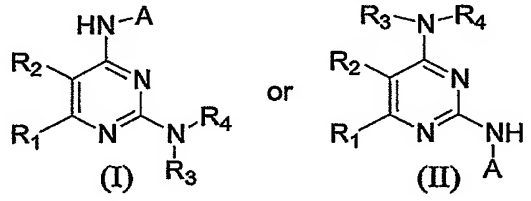
or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

Pharmaceutically acceptable salts of these compounds as well as commonly used prodrugs of these compounds are also within the scope of the invention.

Detailed description

The preferred compounds of the invention are further defined below. In the following description of these preferred compounds, the definitions for the various groups and variables represent the preferred definitions when they differ from those broadly defined above, and are to be understood as independent of each other.

The preferred compounds of the invention are 2,4-diamino-pyrimidine derivative compounds which have the structural formula (I) or (II):



wherein,

R_1 and R_2 are independently selected from the group consisting of hydrogen, halogen, -(C_1-C_3)-alkyl, and -$(CH_2)_nC(=O)OR_7$;

R_3 is hydrogen;

R_4 is selected from the group consisting of:

(a) -(C_1-C_5) linear or branched alkyl,

(b) -(C_5-C_8) cycloalkyl,

(c) -(C_1-C_5)-alkyl-phenyl, and

(d) -phenyl,

wherein (a) - (d) are optionally substituted with one to three substituents selected from the group consisting of:

(1) halogen,

(2) (C_1-C_5) alkoxy-,

(3) -(C_6-C_{10}) aryloxy-,

(4) -(C_1-C_5) linear or branched alkyl optionally substituted by halogen,

(5) -$(CH_2)_nC(=O)R_7$,

(6) -$(CH_2)_nC(=O)OR_7$,

(7) -$(CH_2)_nC(=O)NR_8R_9$, and

(8) a five to six membered saturated or fully unsaturated heterocyclic ring containing one to two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with one substituent selected from the group consisting of oxo, and -(C_1-C_5) alkoxy;

or

R_3 and R_4 form, together with the nitrogen to which they are attached, a saturated five to eight membered heterocyclic ring, which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom and wherein said ring is

optionally substituted with up to two substituents selected from the group consisting of:

(1) cyano,

(2) hydroxy,

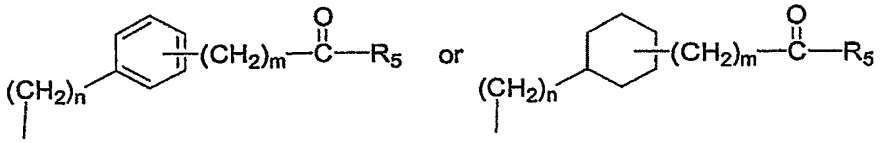
(3) (C_1-C_5) alkoxy-,

(4) -(C_1-C_5) linear or branched alkyl optionally substituted by halogen or (C_1-C_5) alkoxy-,

(5) $-(CH_2)_nC(=O)OR_7$, and

(6) $(CH_2)_nC(=O)NR_8R_9$;

A is either:



R_5 is -OH, $-OR_6$ or $-NR_8R_9$;

R_6 is:

(a) -(C_1-C_5) linear or branched alkyl optionally substituted by halogen, or

(b) phenyl optionally substituted by halogen;

R_7 is:

(f) -(C_1-C_5) linear or branched alkyl, or

(g) phenyl,

wherein (f) and (g) are optionally substituted with halogen;

R_8 and R_9 are independently selected from the group consisting of:

(h) hydrogen,

(i) -(C_1-C_5) linear or branched alkyl, and

(j) -(C_6-C_{10}) aryl;

wherein (i) and (j) are optionally substituted with halogen;

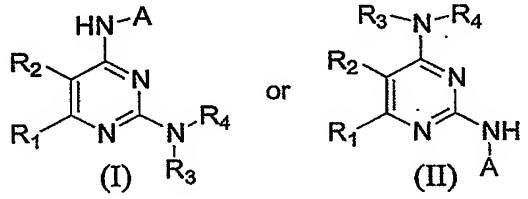
n and m are independently an integer from 0 - 1,

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

Pharmaceutically acceptable salts of these compounds as well as commonly used prodrugs of these compounds are also within the scope of the invention.

The more preferred compounds of the invention are further defined below. In the following description of these more preferred compounds, the definitions for the various groups and variables represent the more preferred definitions when they differ from those broadly defined above, and are to be understood as independent of each other.

The more preferred compounds of the invention are 2,4-diamino-pyrimidine derivative compounds which have the structural formula (I) or (II):



wherein,

R_1 and R_2 are independently selected from the group consisting of hydrogen and halogen,

R_3 is hydrogen;

R_4 is selected from the group consisting of:

(a) -(C_1-C_5) linear or branched alkyl,

(b) -(C_1-C_3)-alkyl-phenyl, and

(c) -phenyl,

wherein (a) - (c) are optionally substituted with one substituent selected from the group consisting of:

(1) halogen,

(2) (C_1-C_5) alkoxy-,

(3) phenoxy,

(6) $-(CH_2)_nC(=O)OR_7$,

(7) $-(CH_2)_nC(=O)NR_8R_9$, and

(8) a five membered saturated or fully unsaturated heterocyclic ring containing one heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with one substituent selected from the group consisting of oxo and $-(C_1-C_5)$ alkoxy;

or

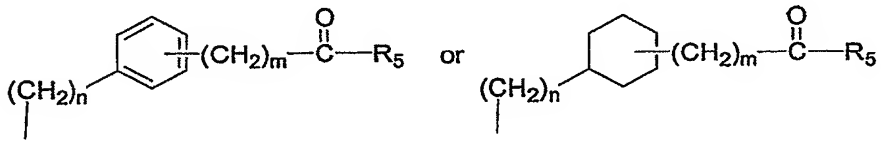
R_3 and R_4 form, together with the nitrogen to which they are attached, a saturated five to six membered heterocyclic ring, which optionally contains one additional heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom and wherein said ring is optionally substituted with up to two substituents selected from the group consisting of:

(1) hydroxy,

(2) $-(C_1-C_5)$ alkoxy,

(3) $-(C_1-C_3)$ linear or branched alkyl optionally substituted by halogen or $-(C_1-C_3)$ alkoxy ;

A is either:



R_5 is -OH, $-OR_6$ or $-NR_8R_9$;

R_6 is:

(a) $-(C_1-C_5)$ linear or branched alkyl optionally substituted by halogen, or

(b) phenyl optionally substituted by halogen;

R_7 is -(C_1-C_5) linear or branched alkyl, optionally substituted with halogen;

R_8 and R_9 are independently selected from the group consisting of:

(h) hydrogen,

(i) -(C_1-C_5) linear or branched alkyl, and

(j) phenyl;

wherein (i) and (j) are optionally substituted with halogen;

n and m are independently an integer from 0 - 1,

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

Pharmaceutically acceptable salts of these compounds as well as commonly used prodrugs of these compounds are also within the scope of the invention.

Salts are especially the pharmaceutically acceptable salts of compounds of formulae (I) or (II) such as, for example, organic or inorganic acid addition salts of compounds of formulae (I) or (II). Suitable inorganic acids include but are not limited to halogen acids (such as hydrochloric acid), sulfuric acid, or phosphoric acid. Suitable organic acids include but are not limited to carboxylic, phosphonic, sulfonic, or sulfamic acids, with examples including acetic acid, trifluoroacetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2- or 3-hydroxybutyric acid, γ-aminobutyric acid (GABA), gluconic acid, glucosemonocarboxylic acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid, methanesulfonic acid, trifluoromethanesulfonic acid, fumaric acid, oxalic acid, succinic acid, adipic acid, pimelic acid, suberic acid, azeiaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids (such as glutamic acid, aspartic acid, N-methylglycine, acetytaminoacetic acid, N-acetylasparagine or N-acetylcysteine), pyruvic acid, acetoacetic acid, phosphoserine, and 2- or 3-glycerophosphoric acid.

In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2}, Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and

aromatic substituted ammonium, and quaternary ammonium cations such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Prodrugs are considered to be any covalently bonded carriers which release the active parent compound of formula (I) or (II) *in vivo*. Formation of prodrugs is well known in the art in order to enhance the properties of the parent compound; such properties include solubility, absorption, biostability and release time (see *"Pharmaceutical Dosage Form and Drug Delivery Systems"* (Sixth Edition), edited by Ansel et al., publ. by Williams & Wilkins, pgs. 27-29, (1995) which is hereby incorporated by reference).

Commonly used prodrugs of the disclosed compounds of formula (I) and (II) are designed to take advantage of the major drug biotransformation reactions and are also to be considered within the scope of the invention. Major drug biotransformation reactions include N-dealkylation, O-dealkylation, aliphatic hydroxylation, aromatic hydroxylation, N-oxidation, S-oxidation, deamination, hydrolysis reactions, glucuronidation, sulfation and acetylation (see *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Tenth Edition), editor Hardman et al., publ. by McGraw-Hill, pages 12-18, (2001), which is hereby incorporated by reference).

Definitions

The term "halogen" as it appears in the specification and claims refers to fluorine, chlorine, bromine, and iodine substituents for the purposes of this invention. When halogen is a possible substituent on an alkyl group, the alkyl may be fully substituted, up to perhalo.

The term "fused bicyclo ring" as it appears in the specification and claims refers to a substituent which is a two ring structure which share two carbon atoms. The bonding between the fused bicyclo ring and the compound and/or atom to which it is attached can be through either of the two rings.

Description of Compositions

The invention also includes pharmaceutical compositions comprising a therapeutically effective amount of one or more of the compounds of formula (I) or (II) or purified stereoisomers or stereoisomer mixtures of the invention, or their salts or prodrugs forms thereof, with a pharmaceutically acceptable ingredient.

The pharmaceutical compositions are prepared so that they may be administered orally, dermally, parenterally, nasally, ophthalmically, otically, sublingually, rectally or vaginally. Dermal administration includes topical application or transdermal administration. Parenteral administration includes intravenous, intraarticular, intramuscular, and subcutaneous injections, as well as use of infusion techniques. One or more compounds of the invention may be present in association with one or more non-toxic pharmaceutically acceptable ingredients and optionally, other active anti-proliferative agents, to form the pharmaceutical composition. These compositions can be prepared by applying known techniques in the art such as those taught in *Remington's Pharmaceutical Sciences* (Fourteenth Edition), Managing Editor, John E. Hoover, Mack Publishing Co., (1970) or *Pharmaceutical Dosage Form and Drug Delivery Systems* (Sixth Edition), edited by Ansel et al., publ. by Williams & Wilkins, (1995), each of which is hereby incorporated by reference.

Commonly used pharmaceutical ingredients which can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal);

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2, F_2ClC-$CClF_2$ and $CClF_3$)

air displacement agents (examples include but are not limited to nitrogen and argon);

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones and styrene-butadiene copolymers);

buffering agents (examples include but are not limited to potassium metaphosphate, potassium phosphate monobasic, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

chelating agents (examples include but are not limited to edetate disodium and edetic acid)

colorants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

clarifying agents (examples include but are not limited to bentonite);

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyethylene 50 stearate);

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

flavorants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

humectants (examples include but are not limited to glycerin, propylene glycol and sorbitol);

levigating agents (examples include but are not limited to mineral oil and glycerin);

oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, saturated or fully unsaturated fatty alcohols, saturated or fully unsaturated fatty esters, saturated or fully unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

plasticizers (examples include but are not limited to diethyl phthalate and glycerin);

solvents (examples include but are not limited to alcohol, corn oil, cottonseed oil, glycerin, isopropyl alcohol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan monopalmitate);

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerin, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc);

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch);

tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powedered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate);

tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium starch glycollate and starch);

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc);

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

tablet/capsule opaquants (examples include but are not limited to titanium dioxide);

tablet polishing agents (examples include but are not limited to carnuba wax and white wax);

thickening agents (examples include but are not limited to beewax, cetyl alcohol and paraffin);

tonicity agents (examples include but are not limited to dextrose and sodium chloride);

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, povidone, sodium alginate and tragacanth); and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, polyethylene sorbitol monooleate, polyoxyethylene sorbitol monooleate, polyoxyethylene stearate,).

Depending on the route of administration, the compositions can take the form of aerosols, capsules, creams, elixirs, emulsions, foams, gels, granules, inhalants, lotions, magmas, ointments, peroral solids, powders, sprays, syrups, suppositories, suspensions, tablets and tinctures.

The compositions of the invention can also have an additional apoptosis inducers as an active ingredient. Examples of known apoptosis inducers (see e.g. Calbiochem's 2001 Signal Transduction Catalog, pages 702-704, the contents of which are incorporated by reference) which can be added to the described invention include but are not limited to A23187, N-Acetyl-L-cysteine, actinomycin D, tyrphostin A9, tyrphostin A25, AG 490, AG 1714, anandamide, anisomycin, aphidicolin, bafilomycin A1, berberine hemisulfate, betulinic acid, bleomycin sulfate, CAFdA, calphostin C, camptothecin, CAPE, chelerythrine

chloride, 2-chloro-2'-deoxyadenosine, 2-chloro-2'-deoxyadenosine 5'-triphosphate, colcemid, cochicine, corticosterone, cycloheximide, cyclophosphamide monohydrate, cyclosporine A, daunorubicin hydrocloride, dexamethasone, 3,3'-diindolylmethane, dolastatin 15, doxorubicin hydrochloride, erbstatin analog, ET-18-OCH_3, etoposide, etoposide phosphate, 5-fluorouracil, folimycin, forskolin, genistein, glycodeoxycholic acid sodium salt, H-7 dihydrochloride, H-89 dihydrochloride, harringtonine, homoharringtonine, 4-hydroxynonenal, 4-hydroxyphenylretinamide, hydroxyurea, indanocine, ionomycin free acid, ionomycin calcium salt, KN-93, methotrexate, mitomycin C, okadaic acid, oligomycin, p53 activator, paclitaxel, phorbol-12-myristate-13-acetate, (pivaloyloxy)methyl butyrate, puromycin dihydrochloride, 1-pyrrolidinecarbodithioic acid ammonium salt, quercetin dihydrate, rapamycin, SNAP, SNOG, sodium butyrate, sodium 4-phenylbutyrate, spermine tetrachloride, D-*erythro*-sphingosine (free base; N-Acetyl-; N,N-dimethyl-; N-hexanoyl-; and N-octanoyl forms), stautosporine, sulfasalizine, sulindac, tamoxifen citrate, 4-hydroxy-(Z)-tamoxifen, thapsigargin, α-toxin, TRAIL, valinomycin, (±)-verapamil hydrochloride, veratridine and vitamin E succinate.

Additional known apoptosis inducers (see Oncogene catalog, the contents of which are incorporated by reference) include:

2β, 3β, 5β, 11α, 14α, 20R, 22R-Heptahydroxycholest-7-en-6-one, dactinomycin, DHAD; 1,4-dihydroxy-5,8-*bis*({2-[(2-hydroxyethyl)amino])-9,10-anthraquinone, 2HCl; N,N-hexamethylenebisacetamide (HMBA); mitoxanthrone, dihydrochloride; MurA; Muristerone A; NSC-301739; SAHA; suberoylanilide, hydroxamic acid; caspase-3 (Ab-4) Monoclonal Antibody; active caspase-7 (Ab-1) Polyclonal Antibody; caspase-12 (Ab-1) Polyclonal Antibody; caspase-12 (Ab-2) Polyclonal Antibody; caspase-13 (Ab-1) Polyclonal Antibody; acinus (Ab-1) Polyclonal Antibody; acinus (Ab-2) Polyclonal Antibody; acinus (Ab-3) Polyclonal Antibody; acinus (Ab-4) Polyclonal Antibody; AIF (Ab-1) Polyclonal Antibody; AIF (Ab-2) Polyclonal Antibody; Phospho-Bad (Ab-1) Polyclonal Antibody; Phospho-Bad (Ab-2) Polyclonal Antibody; Bid (Ab-1) Polyclonal Antibody; Bid (Ab-2) Polyclonal Antiserum; Bid (Ab-3) Polyclonal Antiserum; Bnip3L (Ab-1) Polyclonal Antibody; DRAK1 (Ab-1) Polyclonal Antibody; DRAK2 (Ab-1) Polyclonal Antibody; Fas (Ab-6) Polyclonal Antibody; FLASH (Ab-1) Polyclonal Antiserum; p110 Mitochondrial Protein (Ab-1) Monoclonal Antibody; pTEN (Ab-4) Polyclonal Antibody; Rb Associated Protein 46 (Ab-1) Polyclonal Antibody; Rb Associated Protein 48 (Ab-1) Polyclonal Antibody; RIP (Ab-1)

Polyclonal Antibody; RIP2 (Ab-1) Polyclonal Antibody; Smac/DIABLO (Ab-3) Polyclonal Antibody; TWEAK (Ab-1) Polyclonal Antibody; VDAC (Ab-1) Polyclonal Antibody; Bad Control Proteins; and Fas Ligand Plus™ Recombinant Human Protein.

Optional cancer treatment agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the Merck Index, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other cancer treatment agents suitable for use with the composition of the invention include but are not limited to those compounds acknowldeged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Tenth Edition), editor Hardman et al., publ. by McGraw-Hill, pages 1389-1459, (2001), which is hereby incorporated by reference, such as aminoglutethimide, anastrazole, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, camptothecin, diethylstilbestrol, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, exemestane, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, formestane, hydroxyprogesterone caproate, gemcitabine, idarubicin, IL-2, α-interferon, letrozole, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, oxaliplatin, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, temozolomide, trimethylmelamine, uridine, vinorelbine and vorozole.

Other cancer treatment agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as epothilone.

For all regimens of use disclosed herein for compounds of formulae (I) or (II), the daily oral dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily

dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be understood, however, that the specific dose level for any given patient will depend upon a variety of factors, including, but not limited to the activity of the specific compound employed, the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, rate of excretion, drug combinations, and the severity of the condition undergoing therapy. It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of doses of a compound of formulae (Ia) or (IIa) or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.

Description of Preparative Methods

Abbreviations and Acronyms

The following terms have the indicated meanings.

DCM	dichloromethane
DMF	*N,N*-dimethylformamide
eq	equivalents
EtOAc	ethyl acetate
h	hour
Hex	hexanes

HPLC	high performance liquid chromatography
LC	liquid chromatography
Me	methyl
MP	melting point
MS	mass spectra
NMR	nuclear magnetic resonance
rt	room temperature
TLC	thin layer chromatography
TFA	trifluoroacetic acid

Experimental Section

Analytical data (^{1}H NMR and LC-MS) for all compounds was in accordance with the described sturcutre

Unless otherwise stated, the term 'concentrated under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mm of Hg.

Thin-layer chromatography (TLC) was performed on Whatman® pre-coated glass-backed silica gel 60A F-254 250 μm plates. Visualization of plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, and/or (d) immersion of the plate in a cerium sulfate solution followed by heating. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel.

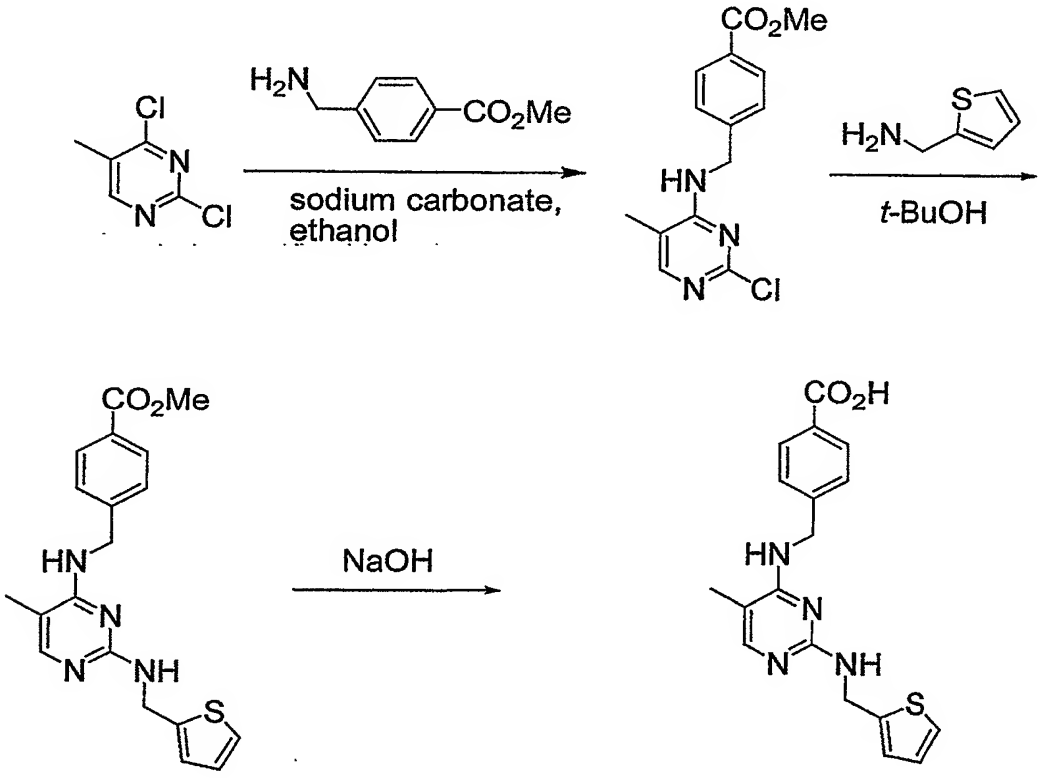
Melting points (mp) were determined using a Thomas-Hoover melting point apparatus or a Mettler FP66 automated melting point apparatus and are uncorrected.

Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric G*N*-Omega 300 (300 MHz) spectrometer with either Me_4Si (δ 0.00) or residual protonated solvent ($CHCl_3$ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Carbon (^{13}C) NMR spectra were measured with a General Electric G*N*-Omega 300 (75 MHz) spectrometer with solvent ($CDCl_3$ δ 77.0; d_3-MeOD; δ 49.0; d_6-DMSO δ 39.5) as standard.

HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonirile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flowrate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

Example 1. Methyl 4-[({5-methyl-2-[(2-thienylmethyl)amino]-4-pyrimidinyl}amino)methyl]benzoate

Example 2. 4-[({5-methyl-2-[(2-thienylmethyl)amino]-4-pyrimidinyl}amino)methyl] benzoic acid.

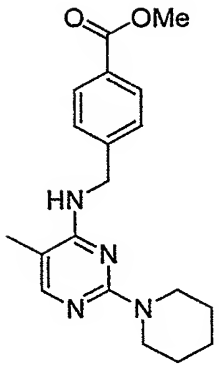


Step 1. Methyl 4-(aminomethyl)benzoate (2.24 g, 11.1 mmol, 1 eq) and sodium carbonate (2.35 g, 22.2 mmol, 2 eq) were added to a solution of 2,4 dichloro-5-methyl pyrimidine (1.81 g, 11.1 mmol, 1 eq) in ethanol were magnetically stirred at rt over a period of 16 h. Next EtOAc (50 mL) was added and this solution was washed (3 x 50 mL) with brine, dried over magnesium sulfate and then filtered. The solution was concentrated under reduced pressure, and purified by column chromatography (30% Hex/EtOAc) to yield methyl 4-{[(2-chloro-5-methyl-4-pyrimidinyl)amino]methyl} benzoate 0.97 g (67%).

Step 2. 2-Thienyl methylamine (393 mg, 0.35 mmol, 4 eq) and concentrated hydrochloric acid (catalytic, 1 drop) were added to a solution of methyl 4-{[(2-chloro-5-methyl-4-pyrimidinyl)amino]methyl}benzoate (252 mg, 0.87 mmol, 1 eq) in *t*-butanol (0.1 M, 5 mL) were magnetically stirred at 100 °C in a sealed tube over a period of 16 h. The excess *t*-butanol was concentrated under reduced pressure. Methylene chloride was added and the solution was washed with saturated aquaeous sodium bicarbonate solution, dried over magnesium sulfate and then filtered. The solution was concentrated under reduced pressure, and purified by column chromatography (50% Hex/EtOAc) to yield methyl 4-[({5-methyl-2-[(2-thienylmethyl)amino]-4-pyrimidinyl}amino)methyl]benzoate 150 mg (47%).). TLC: Rf = 0.17 (1/1 Hex/EtOAc); HPLC/MS: [M+H]+obs = 369.3(ESI+); MP = 94 °C.

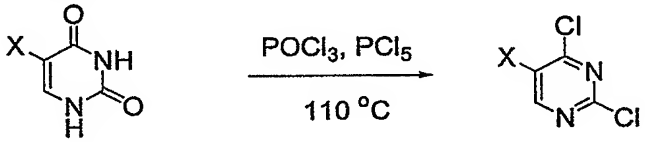
Step 3. Aqueous sodium hydroxide (1N, 20 mL) was added to a solution of methyl 4-[({5-methyl-2-[(2-thienylmethyl)amino]-4-pyrimidinyl}amino)methyl]benzoate (0.18 g, 0.49 mmol) in methanol (10 mL). The mixture was stirred rt for 24 h. The mixture was adjusted to pH 5 with aqueous hydrochloric acid (1N) and the methanol was concentrated under reduced pressure. The resulting solid was filtered, rinsed with deionized water, and let dry *in vacuo* to yield 4-[({5-methyl-2-[(2-thienylmethyl)amino]-4-pyrimidinyl} amino)methyl]benzoic acid 0.4 g (20%).). TLC: Rf = 0.10 (1/1 Hex/EtOAc); HPLC/MS: [M+H]+obs = 355.2 (ESI+); MP > 225 °C.

Example 3. Methyl 4-({[5-methyl-2-(1-piperidinyl)-4-pyrimidinyl]amino}methyl) benzoate.



A solution of methyl 4-{[(2-chloro-5-methyl-4-pyrimidinyl)amino]methyl}benzoate (620 mg, 2.10 mmol) and piperidine (1.09 g, 12.80 mmol) in dry DMF (11 mL) was stirred at rt for 72 h, then at 70 °C for 6 h. The reaction was quenched with water (100 mL) and extracted with EtOAc (2 x 100 ml). The organic layers were washed with water (2 x 50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give the product as a white solid in 87% yield (620 mg, 1.82 mmol). TLC: Rf = 0.67 (EtOAc); HPLC/MS: [M+H]+obs = 341 (ESI+); MP = 92 °C.

Preparation of Dichloropyrimidine Intermediates



X = F, Cl

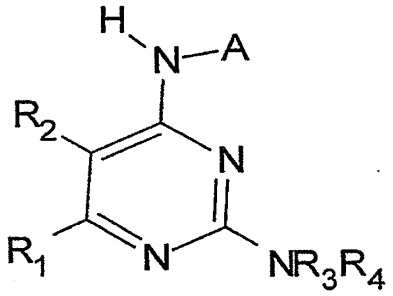
The desired uracil (1 eq) was dissolved in phosphorous oxychloride (1.1 M) and phosphorous pentachloride (1.1 eq) and stirred at 110 °C over a period of 16 h. The reaction was cooled, excess $POCl_3$ was removed under reduced pressure and the resulting residue was quenched with ice water. The solution was poured into a separatory funnel and extracted with ethyl acetate (2x). The combined organics were washed with saturated. $NaHCO_3$ followed by sataturated. NaCl, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting yellow oil was used without purification.

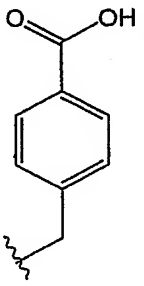
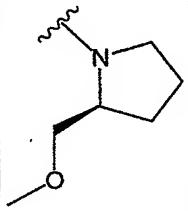
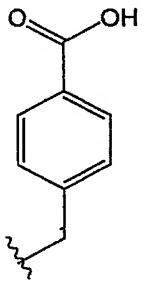
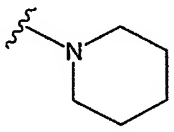
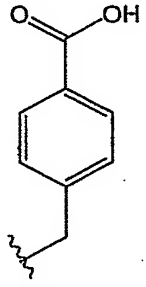
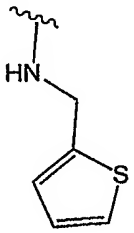
Examples 4 - 29 in Table 1 were synthesized according to the above methods or by using other synthetic methods known in the art such as those described in the monograph series "The Chemistry of Heterocyclic Compounds", edited by Weissberger, *The Pyrimidines*, edited by D.J. Brown, publ. by Interscience Publishers, (1962) or the monograph series "The

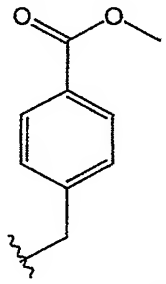
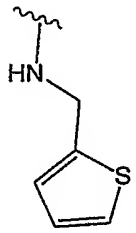
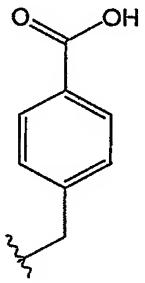
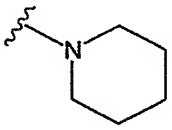
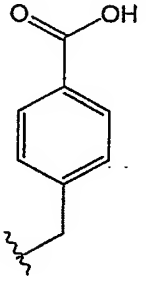
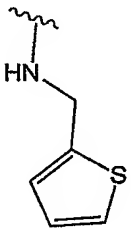
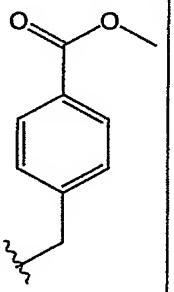
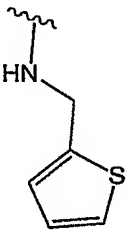
Chemistry of Heterocyclic Compounds", edited by Weissberger and Taylor, *The Pyrimidines - Supplement I*, edited by D.J. Brown, publ. by Interscience Publishers, (1970), and Vol. 52, *The Pyrimidines*, edited by D.J.Brown, Interscience Publishers, (1994), each of which is incorporated in its entirety by reference.

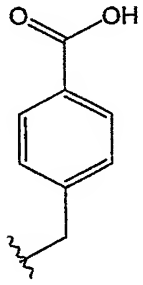
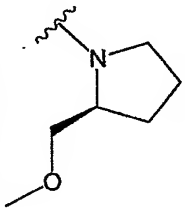
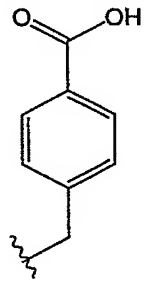
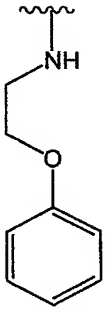
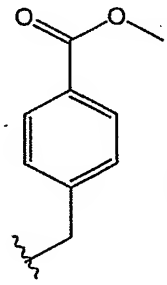
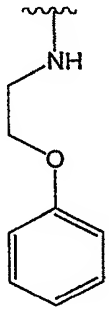
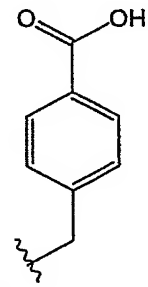
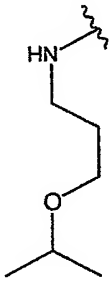
5

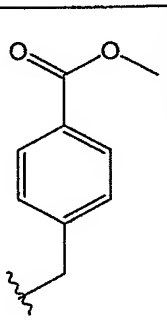
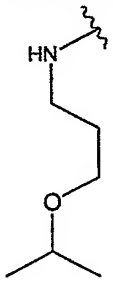
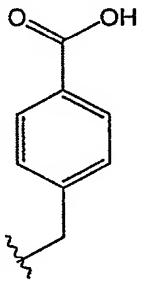
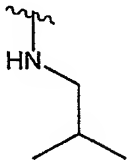
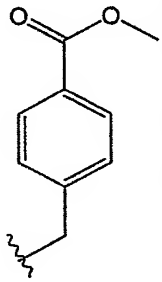
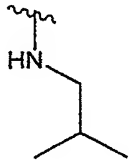
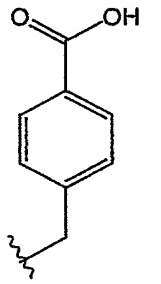
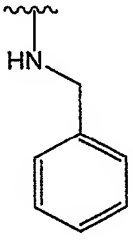
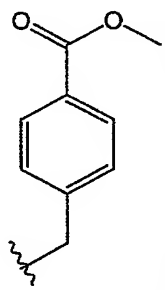
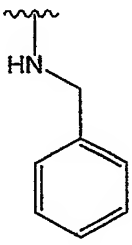
Table 1. 2,4-Diamino-Pyrimidine Compounds

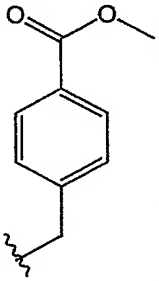
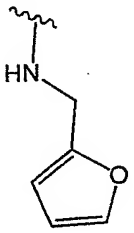
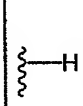
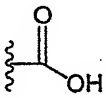
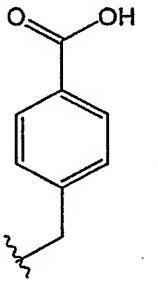
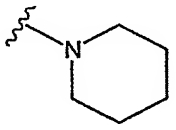
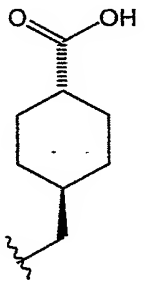
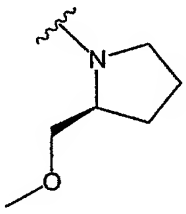
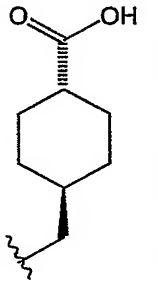
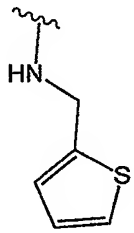


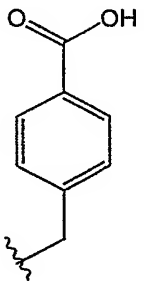
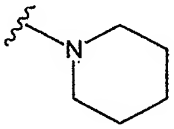
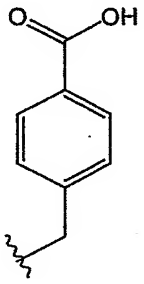
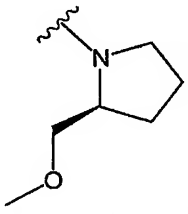
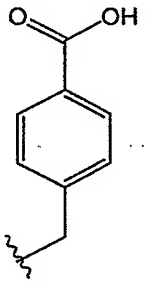
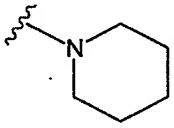
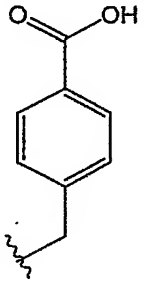
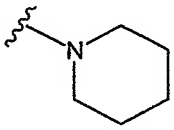
Ex.	R1	R2	A	NR3R4	TLC/HPLC	MS $(MH)^+$	MP (°C)
4					TLC Rf = 0.38 (95/5 DCM/MeOH)	377	
5					TLC Rf = 0.26 (95/5 DCM/MeOH)	347	
6					TLC Rf = 0.14 (95/5 DCM/MeOH)	375	

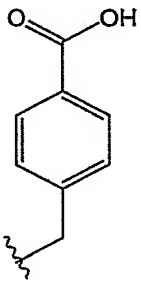
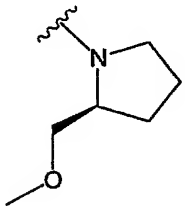
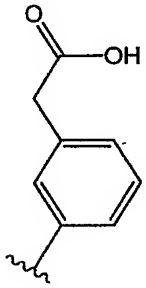
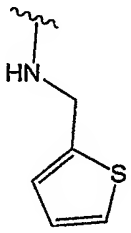
Ex.	R1	R2	A	NR3R4	TLC/HPLC	MS $(MH)^+$	MP (°C)
7					TLC Rf = 0.44 (3/2 Hexane/EtOAc)	389	
8					TLC Rf = 0.14 (9/1 DCM/MeOH)	331	
9					TLC Rf = 0.53 (9/1DCM/MeOH)	359	
10					TLC Rf = 0.31 (3/2 Hexane/EtOAc)	373	

Ex.	R1	R2	A	NR3R4	TLC/HPLC	MS $(MH)^+$	MP (°C)
11	H	F			TLC Rf = 0.56 (9/1 DCM/MeOH)	361	
12	H	Cl			TLC Rf = 0.75 (9/1 DCM/MeOH)	399	
13	H	Cl			TLC Rf = 0.41 (3/2 Hexane/EtOAc)	413	
14	H	Cl			TLC Rf = 0.50 (9/1 DCM/MeOH)	379	

Ex.	R1	R2	A	NR3R4	TLC/HPLC	MS (MH)$^+$	MP (^{o}C)
15	H	Cl			TLC Rf = 0.39 (3/2 Hexane/EtOAc)	393	
16	H	Cl			TLC Rf = 0.44 (9/1 DCM/MeOH)	335	
17	H	Cl			TLC Rf = 0.47 (3/2 Hexane/EtOAc)	349	
18	H	Cl			TLC Rf = 0.41 (9/1 DCM/MeOH)	369	
19	H	Cl			TLC Rf = 0.39 (3/2 Hexane/EtOAc)	383	

Ex.	R1	R2	A	NR3R4	TLC/HPLC	MS $(MH)^+$	MP (°C)
20					TLC Rf = 0.25 (3/2 Hexane/EtOAc)	373	
21					HPLC RT = 1.96 (98%H_2O-98%CH_3CN)	357	
22					TLC Rf = 0.45 (1/1 Hexane/EtOAc)	429.3	
23					TLC Rf = 0.15 (1/1 Hexanes/EtOAc)	425.1	

Ex.	R1	R2	A	NR3R4	TLC/HPLC	MS $(MH)^+$	MP (°C)
24	H	Br			TLC Rf = 0.20 (1/1 Hexane/EtOAc)	391.4	206-8
25	H	Br			TLC Rf = 0.20 (1/1 Hexane/EtOAc)	421.3	
26	H	Me				327	167
27	Me	H				327	>240 dec.

Ex.	R1	R2	A	NR3R4	TLC/HPLC	MS $(MH)^+$	MP (°C)
28					TLC Rf = 0.10 (1/1 Hexane/EtOAc)	357.4	
29					TLC Rf = 0.10 (1/1 Hexane/EtOAc)	420.3	168-170

Description of Inhibiting Prolylpeptidase, Inducing Apoptosis and Treatment of Cancer

Apoptosis (programmed cell death) is an essential process in the development and maintenance of homeostasis in an organism (1). The growth fraction of a tumor is governed by the rate of cellular division as well as the rate of cell death: if the rate of division exceeds that of cell death, then net tumor expansion occurs. Importantly, net growth rates of tumors do not generally correlate directly with the rate of cell division within the tumor, as assessed by the abundance of mitotic figures. Hence, aberrant apoptotic rate plays an important role in tumor growth and expansion (2, 3).

Studies have demonstrated that cells transfected with either *myc* or *ras* oncogenes exhibit altered proliferation and apoptotic rates (4, 5). Transfectant cell lines that displayed elevated rates of *both* cell division and apoptosis lead to established tumors with reduced efficiency, compared to transfectant lines that displayed an elevated rate of cell division and reduced rate of apoptosis. Moreover, tumors with comparable mitotic indices exhibit radically different net growth rates depending on whether the basal apoptotic rates are low (yielding high tumor growth rates) or high (yielding low tumor growth rates). For example, low apoptotic rates are thought to drive the observed net growth rates observed in prostate cancer (6). Hence, targets that regulate apoptotic pathways in tumor cells should provide important points for novel therapeutic intervention and, should lead to an improved therapeutic effect (7).

Proteases are attractive cancer drug targets since they are known to regulate apoptotic signal transduction (8, 9). For example, work on apoptosis initiated by specific inhibitors of the proteasome complex has been reported in the literature, where lactacystin and other proteasome inhibitors are shown to cause apoptosis in a number of cell lines (10, 11).

Recent publications have identified prolylpeptidase (QPP) as an intracellular protease involved in the repression of apoptosis and, as such, prolylpeptidase is thought to be an anti-apoptotic factor (12, 13). Prolylpeptidase is a serine protease that is irreversibly inactivated by diispropyl-fluorophosphate (DFP) through covalent modification of Ser154 (12) and unpublished data. It is the only known human serine protease that is fully active without additional post-translational removal of inhibitory peptide. In addition, the enzyme is localized to novel non-lysosomal cytosolic vesicles (14). Recombinant prolylpeptidase as

well as prolylpeptidase purified from natural sources are active as dimeric proteins (106 kDa), based on size exclusion chromatography, although the gene encodes a putative enzyme with a predicted mass of 58 kDa (15).

Active prolylpeptidase has been identified in a number of solid tumor cell lines of different histological types including those from colon (HCT116 and DLD1), prostate (PC3), and breast (MDA-MB-435). In addition, expression data for prolylpeptidase mRNA shows a very limited distribution across adult human tissues, with highest levels observed in the testis, and moderate levels in prostate, skeletal muscle and brain. Increased expression of prolylpeptidase mRNA in human tumor specimens and the published biological data on the enzyme suggest that prolylpeptidase plays an important role in tumor cell growth or survival. In summary, these data suggest that selective inhibition of prolylpeptidase activity in tumor cells could lead to increased apoptotic rates and growth inhibition.

Described below are the results of prolylpeptidase inhibition assays and apoptosis induction assays which show the effect of the applicants described compounds.

The prolylpeptidase enzyme used in the assay protocol cited below was described by Kapeller-Libermann et al. (U.S. Serial No. 09/345,469, the contents of which is hereby incorporated by reference; see also WO 01/00812).

Prolylpeptidase Assay Protocol

Test compounds were diluted serially 1:5 in 5% DMSO/95% water and 5 µL was added to give 100 µL as a final volume to a well containing prolylpeptidase enzyme in buffer. Drug had a final concentration ranging from 10 µM to 0.12 µM. The Ala-Pro-AFC dipeptide substrate (AFC is 7-amino-4-trifluoro-methylcoumarin) in MTEN buffer was used at a final concentration of 200 µL and the reaction was initiated with 10 nM final concentration of recombinant prolylpeptidase. The reaction was allowed to proceed for 20 min at room temperature and quenched with 20 µL of 1 M Glycine-HCl pH 2.5. The 96 well plates were read as an endpoint assay at an excitation of 400 nm and emission of 505 nm. The final DMSO concentration was 0.25% in the assay.

Ala-Pro-AFC is a dipeptide substrate with a conjugated AFC fluorophore at the C-terminus. Hydrolysis of the dipeptide substrate releases free AFC which is excited at 400 nm and emission of 505 nm in a spectrofluorometer.

Assay buffer is 50 mM MTEN Buffer pH 4.5 (50 mM MES, 25 mM Tris, 25 mM ethanolamine, 100 mM NaCl). Enzyme storage buffer was 50 mM Tris pH 7.0, 50% glycerol and was stored at -80 °C. It was diluted in assay buffer just prior to initiation of the assay.

All example compounds of formula (I) and (II) were tested in the above prolylpeptidase assay and were found to inhibit prolylpeptidase at or below a concentration of 10 μM.

Multiparameter Apoptosis Assay

The induction of apoptosis by prolylpeptidase inhibitors was measured in whole cells using the multiparameter apoptosis assay (MPA). The assay uses the ArrayScan II (Cellomics Inc. Pittsburgh, PA) and the MPA application software to simultaneously measure three parameters of apoptosis 1.) nuclear fragmentation 2.) actin content and 3.) mitochondrial potential. Test compounds were dissolved in 100% DMSO and diluted serially 1:2 in DMEM with 10% fetal calf serum (final DMSO concentration 0.25%) and added to HCT-116 cells growing in 96-well tissue culture plates. The final drug concentrations ranged from 25 μM to 0.39 μM. Cells were exposed to the test compound for either one or 24 hours depending on the experiment. The MPA assay was run according to the manufactures' protocol. The % of control for each compound concentration is determined using the formula; %Control = (((Experimental Units)-Blank Units)/Units from untreated Control-Blank Units)*100. A curve is fitted and a value for Y=50% (IC_{50}) using the formula Y=A+((B-A)/(1+(((B-E)(X/C)^D)/(E-A))). The average of the IC_{50} values for nuclear fragmentation, actin content and mitochondria index is used as the MPA IC_{50}.

Example 1 was tested in the above apoptosis assay and was found to induce apoptosis at or below a concentration of 25 μM.

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(All references cited are hereby incorporated by reference)

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13. Chiravuri, M. and Huber, B. T. Aminodipeptidase inhibitor-induced cell death in quiescent lymphocytes: a review, Apoptosis. *5:* 319-22., 2000.

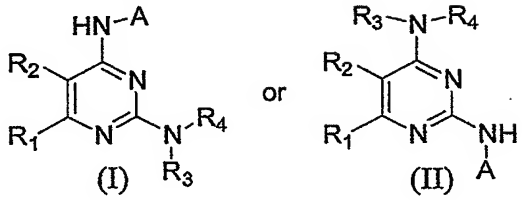
14. Chiravuri, M., Agarraberes, F., Mathieu, S. L., Lee, H., and Huber, B. T. Vesicular localization and characterization of a novel post-proline-cleaving aminodipeptidase, quiescent cell proline dipeptidase, J Immunol. *165:* 5695-702., 2000.

15. Chiravuri, M., Lee, H., Mathieu, S. L., and Huber, B. T. Homodimerization via a leucine zipper motif is required for enzymatic activity of quiescent cell proline dipeptidase, J Biol Chem. *275:* 26994-9., 2000.

Other embodiments of the invention will be apparent to the skilled in the art from a consideration of this specification or practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A compound of formula:



wherein,

R_1 and R_2 are independently selected from the group consisting of hydrogen, halogen, hydroxy, -(C_1-C_3)-alkyl, -(C_1-C_5) alkoxy- and -$(CH_2)_nC(=O)OR_7$;

R_3 is hydrogen;

R_4 is selected from the group consisting of:

(a) -(C_1-C_5) linear or branched alkyl,

(b) -(C_3-C_{10}) cycloalkyl,

(c) -(C_1-C_5)-alkyl-(C_6-C_{10}) aryl, and

(d) -(C_6-C_{10}) aryl,

wherein (a) - (d) are optionally substituted with one to three substituents selected from the group consisting of:

(1) amino,

(2) cyano,

(3) halogen,

(4) hydroxy,

(5) nitro,

(6) (C_1-C_5) alkoxy-,

(7) -(C_6-C_{10}) aryloxy-,

(8) -(C_1-C_5) alkylamino,

(9) -(C_1-C_5) linear or branched alkyl optionally substituted by halogen,

(10) $-(CH_2)_nC(=O)R_7$,

(11) $-(CH_2)_nC(=O)OR_7$,

(12) $-(CH_2)_nC(=O)NR_8R_9$,

(13) a four to eight membered saturated or fully unsaturated heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, (C_1-C_5) alkoxy-, -(C_1-C_5) alkylamino and (C_1-C_5) linear or branched alkyl optionally substituted by halogen; and

(14) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated four to eight membered heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom, and the other ring is a saturated or fully unsaturated three to eight membered carbocycle,

or

R_3 and R_4 form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom and wherein said ring is optionally substituted with up to three substituents selected from the group consisting of:

(1) amino,
(2) cyano,
(3) halogen,
(4) hydroxy,
(5) nitro,
(6) (C_1-C_5) alkoxy-,
(7) -(C_1-C_5) alkylamino,

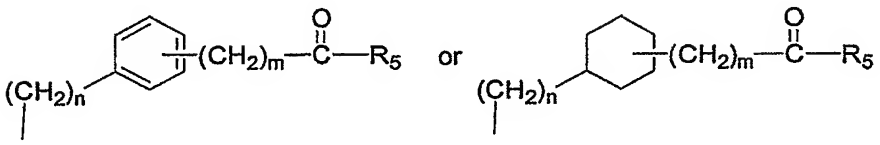
(8) -(C_1-C_5) linear or branched alkyl optionally substituted by halogen or (C_1-C_5) alkoxy-,

(9) -$(CH_2)_nC(=O)R_7$,

(10) -$(CH_2)_nC(=O)OR_7$, and

(11) $(CH_2)_nC(=O)NR_8R_9$;

A is either:



R_5 is -OH, -OR_6 or -NR_8R_9;

R_6 is:

(a) -(C_1-C_5) linear or branched alkyl optionally substituted by halogen, or

(b) -(C_6-C_{10}) aryl optionally substituted by halogen;

R_7 is:

(e) hydrogen,

(f) -(C_1-C_5) linear or branched alkyl, or

(g) -(C_6-C_{10}) aryl,

wherein (f) and (g) are optionally substituted with halogen;

R_8 and R_9 are independently selected from the group consisting of:

(h) hydrogen,

(i) -(C_1-C_5) linear or branched alkyl, and

(j) -(C_6-C_{10}) aryl;

wherein (i) and (j) are optionally substituted with halogen;

n and m are independently an integer from 0 - 1,

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

2. A pharmaceutical composition for the inhibition of prolylpeptidase, induction of apoptosis or the treatment of cancer which comprises a therapeutically effective amount of one or more compounds of claim 1 and a pharmaceutically acceptable ingredient.

3. The pharmaceutical composition of claim 2 which further comprises an additional agent which induces apoptosis.

4. The pharmaceutical composition of claim 3 wherein the agent is selected from the group consisting of A23187, N-Acetyl-L-cysteine, actinomycin D, tyrphostin A9, tyrphostin A25, AG 490, AG 1714, anandamide, anisomycin, aphidicolin, bafilomycin A1, berberine hemisulfate, betulinic acid, bleomycin sulfate, CAFdA, calphostin C, camptothecin, CAPE, chelerythrine chloride, 2-chloro-2'-deoxyadenosine, 2-chloro-2'-deoxyadenosine 5'-triphosphate, colcemid, cochicine, corticosterone, cycloheximide, cyclophosphamide monohydrate, cyclosporine A, daunorubicin hydrocloride, dexamethasone, 3,3'-diindolylmethane, dolastatin 15, doxorubicin hydrochloride, erbstatin analog, ET-18-OCH_3, etoposide, etoposide phosphate, 5-fluorouracil, folimycin, forskolin, genistein, glycodeoxycholic acid sodium salt, H-7 dihydrochloride, H-89 dihydrochloride, harringtonine, homoharringtonine, 4-hydroxynonenal, 4-hydroxyphenylretinamide, hydroxyurea, indanocine, ionomycin free acid, ionomycin calcium salt, KN-93, methotrexate, mitomycin C, okadaic acid, oligomycin, p53 activator, paclitaxel, phorbol-12-myristate-13-acetate, (pivaloyloxy)methyl butyrate, puromycin dihydrochloride, 1-pyrrolidinecarbodithioic acid ammonium salt, quercetin dihydrate, rapamycin, SNAP, SNOG, sodium butyrate, sodium 4-phenylbutyrate, spermine tetrachloride, D-*erythro*-sphingosine (free base; N-Acetyl-; N,N-dimethyl-; N-hexanoyl-; and N-octanoyl forms), stautosporine, sulfasalizine, sulindac, tamoxifen citrate, 4-hydroxy-(Z)-tamoxifen, thapsigargin, α-toxin, TRAIL, valinomycin, (±)-verapamil hydrochloride, veratridine and vitamin E succinate.

5. The pharmaceutical composition of claim 2 which further comprises an additional agent for the treatment of cancer.

6. The pharmaceutical composition of claim 5 wherein said additional agent for the treatment of cancer is selected from the group consisting of asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, vindesine, aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, vinorelbine, epothilone, irinotecan, raloxifen and topotecan.

7. A method of inhibiting prolylpeptidase which comprises administering to a patient in need thereof a therapeutically effective amount of the compound of claim 1.

8. A method of inhibiting prolylpeptidase which comprises administering to a patient in need thereof a therapeutically effective amount of the composition of claim 2.

9. A method of inducing apoptosis which comprises administering to a patient in need thereof a therapeutically effective amount of the compound of claim 1.

10. A method of inducing apoptosis which comprises administering to a patient in need thereof a therapeutically effective amount of the composition of claim 2.

11. A method of inducing apoptosis which comprises administering to a patient in need thereof a therapeutically effective amount of the composition of claim 3.

12. A method of inducing apoptosis which comprises administering to a patient in need thereof a therapeutically effective amount of the composition of claim 4.

13. A method of treating cancer which comprises administering to a patient in need thereof a therapeutically effective amount of the compound of claim 1.

14. A method of treating cancer which comprises administering to a patient in need thereof a therapeutically effective amount of the composition of claim 2.

15. A method of treating cancer which comprises administering to a patient in need thereof a therapeutically effective amount of the composition of claim 5.

16. A method of treating cancer which comprises administering to a patient in need thereof a therapeutically effective amount of the composition of claim 6.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/41146

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/506 C07D409/12 C07D403/12 C07D239/48 C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 64656 A (BREAULT GLORIA ANNE ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) example 12 claim 1 page 1, line 25 - line 31	1,2
X	WO 01 64655 A (PEARSON STUART ERIC ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) precursors of compounds: 1-10; 11-20; 21-30; 60-66; 71-85; 86-90; 99-100 and 109	1
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	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 March 2003	01/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fanni, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/41146

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 945 443 A (JANSSEN PHARMACEUTICA NV) 29 September 1999 (1999-09-29) example 100 claim 1	1,2
X	EP 0 002 341 A (BOETTCHER BARRY ;WALKER WILLIAM RAYMOND (AU); WHITEHOUSE MICHAEL W) 13 June 1979 (1979-06-13) examples 9-12	1
X	HURT C A R ET AL: "THE SYNTHESIS OF PYRIMIDOQUINAZOLONES" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, no. 1, SUPPL 7, 1966, pages 227-231, XP001029239 ISSN: 0040-4020 page 230-232 cf acetyl derivatives of disclosed compounds	1
X,P	WO 02 096888 A (SCHERING AG) 5 December 2002 (2002-12-05) examples 143,146,151,153,155,158,172 claim 1	1,2
A	WO 01 16301 A (UNIV TUFTS ;HUBER BRIGITTE T (US); UNDERWOOD ROBERT H (US)) 8 March 2001 (2001-03-08) claim 1	7-16

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/41146

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7-16
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 7-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 7-16

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/41146

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/41146

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		US 2003027282 A1	06-02-2003